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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,783	07/25/2003	Martin Friedlander	TSRI-900.1	5526

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/628,783	FRIEDLANDER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,52-56,58,59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50, 52-56, 58-59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 9/15/05 has been entered.

Amended claims 50, 52-56, 58-59 and 61 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 USC 102(e) as being anticipated by Wilson et al. (US Patent 6,767,737) is withdrawn in light of Applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 55-56, 58-59 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the Office Action mailed on 3/16/05 (pages 2-8).

Response to Arguments

Applicant's arguments related in part to the above rejection in the Amendment filed on 9/15/05 (pages 4-6) have been fully considered, but they are not found persuasive.

1. With respect to the issue on how to make and use the claimed invention, Applicant argues that the Office Action clearly applies the wrong standard for utility to the present method claims, and that the threshold of utility is not high.

Please note that enablement requires the specification to teach how to make and/or use the claimed invention, and the rejection is an enablement rejection and NOT a utility rejection. When read in light of the specification, the sole intended purpose for the methods as claimed is to attain therapeutic effects for ocular treatments (see specification, page 1, lines 15-18; and Summary of the invention), and the instant specification is not enabled for the reasons already set forth in the previous Office Action.

2. Applicant further argues that the Office action seems to equate the presently claimed methods with methods of treating or, more specifically methods of "curing" a disease, and that characterization is incorrect. The amended claims are not directed to treatment of a disease per se. Applicant also argues that inhibition of angiogenesis is a tool, which can be used therapeutically or can be used as a research tool to induce vascular changes in the eye of a mammal (e.g., to model a vascular disease or to provide a screening tool for vascular promoters, and the like). The

specification clearly demonstrated the effects of inhibiting angiogenesis in the eye and delivering a gene encoding an antiangiogenic peptide to the eye.

The enablement rejection of record does not require any cure for any disease as alleged by Applicant (Please re-read the rejection of record). With respect to Applicant's argument that the claimed methods can be used for uses other than for attaining therapeutic effects or for treatment purposes such as a research tool to model a vascular disease or a screening tool for vascular promoters, and the like, Examiner would like to point out that these non-treatment uses are not taught or contemplated by Applicant in the originally filed specification. Please point out the specific page number and the specific line numbers where such uses are taught or contemplated by Applicant. As already noted above, when read in light of the specification, the sole intended purpose for the methods as claimed is to attain therapeutic effects for ocular treatments (see specification, page 1, lines 15-18; and Summary of the invention).

3. Applicant argues that even if, *arguendo*, the claims are characterized as therapeutic methods for treating an ocular disease, such treatment can be useful despite some potential adverse side effects in some patients. There is no requirement in the law that a treatment must be a "cure".

Once again, the enablement rejection of record does not require any cure for any disease as alleged by Applicant. As pointed out in the previous Office Action the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain any therapeutic effects as a result of intravitreally injecting a lineage negative hematopoietic

stem cell population transfected with T2-TrpRS gene into a patient, or a treated mammal. Additionally, there is absolutely no correlation between the attainment of significant abnormalities in primary and secondary retinal vascular plexuses in mice treated with T2-TrpRS transfected Lin negative HSC composition with any therapeutic effects contemplated by Applicants. It is uncertain how the expression of the anti-angiogenic peptide T2-TrpRS or any other anti-angiogenic peptides is turned off when it is no longer needed without adversely affecting the structure and functionality of the eye of the treated patient or mammal? Nor is it clear that angiostatic expressing cells can function in models of hypoxia-induced pathological retinal neovascularization or in other models of pathological vessel loss in the retina. The physiological art and the gene therapy art are also recognized to be unpredictable. In light of the totality of prior art at the effective filing date of the present application, coupled with the lack of the sufficient guidance provided by the instant specification it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

4. With respect to the McFarland article cited by the examiner, Applicant argues basically that the article is inapt because it does not even address the use of transfected stem cells. With respect to the Smith article, Applicant argues that some portions of the article reflect positively on the use of the novel stem cells disclosed by Otani et al, and therefore it clearly supports the patentability of the present claims.

The post-filing McFarland article demonstrates clearly that the attainment of any therapeutic effect in treating any ocular disease via gene therapy (encompassing *ex*

vivo gene therapy) remains to be unpredictable even in 2004, let alone at the effective filing date of the present application (7/25/02). The mere statement "The use of stem cells as drug delivery vehicles **has the potential** to selectively and potently deliver drugs to the back of the eye..." does not indicate that any therapeutic effect can be attained by the methods as claimed.

Thus in light of the detailed analysis of the Wands factors set forth in the Office Action mailed on 3/16/05, the instant amended claims 55-56, 58-59 and 61 are still rejected under 35 U.S.C. 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Claim 56 recites the limitation "the transfected lineage negative hematopoietic stem cell population" in lines 1-2 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because in the method of claim 55 from which claim 56 is dependent, there is no recitation of any transfected lineage negative hematopoietic stem cell population. Accordingly, the metes and bounds of the claim are not clearly determined.

Claim Rejections - 35 USC § 103

Amended claims 50 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al (US Patent 6,767,737) in view of Schimmel et al. (US 2003/0017564 with the effective filing date of 2/23/2001) for the same reasons already set forth in the Office Action mailed on 3/16/05 (pages 10-13).

Wilson et al disclose the preparation of a CD34+ FGFR+ cell population having a "primitive phenotype" which also expresses c-kit marker (52% of cells) and CD31 (70% of cells) from human bone marrow, cord blood, general circulation or embryonic cells (see abstract; col. 3, lines 55-62; col. 6, lines 33-59; Figure 1; and examples). Wilson et al further teach that the isolated primitive stem cell population contains endothelial and/or stromal stem cells (see Summary of the invention). Additionally, Wilson et al teach that the stem cells can be used to target the delivery of angiostatic agents and anti-tumor agents to the rapidly proliferating vascular bed associated with tumors (col. 9, lines 7-15) or genetically engineered to secrete proteins such as t-PA, clotting factors or adenosine deaminase (col. 9, lines 26-59).

However, Wilson et al. do not specifically teach that their stem cell population is transfected with a gene encoding a therapeutically useful peptide which is an anti-angiogenic peptide or an anti-angiogenic protein fragment, even though they disclosed that the stem cells can be used to target the delivery of angiostatic agents and anti-tumor agents to the rapidly proliferating vascular bed associated with tumors (col. 9, lines 7-15).

However at the effective filing date of the present application, Schimmel et al already disclose that truncated Tryptophanyl-tRNA synthetase (TrpRS) polypeptides, e.g., mini TrpRS, T1 and T2) are potent polypeptides for the inhibition of angiogenesis (Figures 1, 3, 4 and examples), as well as recombinant expression vectors encoding the same (see Summary of the invention, page 2, col. 2). Schimmel et al further teach that cells can be transfected *in vivo*, *ex vivo* or *in vitro* with their recombinant vectors, and following *ex vivo* or *in vitro* transfection, the cells can be implanted into a host (page 11, paragraph 0121). Schimmel et al also teach that angiostatic trpRs therapy can be used to oppose the angiogenic activity of endogenous and exogenous angiogenic factors, and to prevent further growth or even regress solid tumors, since angiogenesis and neovascularization are essential steps in solid tumor growth (page 12, paragraph 0132).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the teachings of Wilson et al. by genetically modifying their stem cell population with recombinant expression vectors encoding truncated fragments of TrpRS to target these potent angiostatic peptides to the rapidly proliferating vascular bed associated with tumors to inhibit the growth of solid tumors in light of the teachings of Schimmel et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the truncated fragments of TrpRS have been demonstrated by Schimmel et al. to be potent angiostatic peptides, and that they are also specifically taught to be used to oppose the angiogenic activity of endogenous and exogenous angiogenic factors, and to prevent further growth or even regress solid tumors by *in vivo* and *ex vivo* gene approaches.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Wilson et al., Schimmel et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments related in part to the above rejection in the Amendment filed on 9/15/05 (pages 7-8) have been fully considered, but they are not found persuasive.

Applicant argues basically that Wilson et al. do not teach or suggest transfecting stem cells with any antiangiogenic peptide, and that Schimmel et al. do not teach or suggest transfecting stem cells with a gene encoding T2-TrpRS. Additionally, Applicants argue that one of ordinary skill in the art would not have had a reasonable expectation of success for combining the teachings of Wilson et al. and Schimmel et al to arrive at the presently claimed stem cell lines, particularly nothing in the references that would have provided a reasonable expectation of producing transfected stem cells having the unexpected astrocyte targeting properties of the claimed stem cells.

Firstly, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so

found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Wilson et al teach clearly that a CD34+ FGFR+ cell population having a "primitive phenotype" which also expresses c-kit marker (52% of cells) and CD31 (70% of cells) from human bone marrow, cord blood, general circulation or embryonic cells, can be used to target the delivery of angiostatic agents and anti-tumor agents to the rapidly proliferating vascular bed associated with tumors (col. 9, lines 7-15). Schimmel et al teach that truncated Tryptophanyl-tRNA synthetase (TrpRS) polypeptides, e.g., mini TrpRS, T1 and T2) are potent polypeptides for the inhibition of angiogenesis (Figures 1, 3, 4 and examples), as well as recombinant expression vectors encoding the same, and cells can be transfected *in vivo*, *ex vivo* or *in vitro* with their recombinant vectors, and following *ex vivo* or *in vitro* transfection, the cells can be implanted into a host (page 11, paragraph 0121). Schimmel et al also teach that angiostatic trpRs therapy can be used to oppose the angiogenic activity of endogenous and exogenous angiogenic factors, and to prevent further growth or even regress solid tumors, since angiogenesis and neovascularization are essential steps in solid tumor growth (page 12, paragraph 0132). Additionally, as noted in the previous rejection an ordinary skilled artisan would have been motivated to combine the references because the truncated fragments of TrpRS have been demonstrated by Schimmel et al. to be potent angiostatic peptides, and that they are also specifically taught to be used to oppose the angiogenic activity of

endogenous and exogenous angiogenic factors, and to prevent further growth or even regress solid tumors by *in vivo* and *ex vivo* gene approaches.

Secondly, it is unclear what is unpredictable with respecting to the transfection or transforming the isolated stem cell population of Wilson et al. with recombinant vectors expressing truncated TrpRS polypeptides *in vitro or ex vivo*? This is a well-established procedure.

Thirdly, with respect to the issue that transfected stem cells having the unexpected astrocyte targeting properties, it is noted that transfected stem cells resulting from the combined teachings of Wilson et al. and Schimmel et al. are indistinguishable from the transfected stem cells of the presently claimed invention. Furthermore, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Accordingly, the instant claims are still rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al (US Patent 6,767,737) in view of Schimmel et al. (US

2003/0017564 with the effective filing date of 2/23/2001) for the same reasons already set forth in the Office Action mailed on 3/16/05 (pages 10-13).

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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CELIAN QIAN
PATENT EXAMINER